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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,945	02/20/2001	Peter Matthiessen	20560-27	5134

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EXAMINER
SNEDDEN, SHERIDAN

ART UNIT	PAPER NUMBER
1653	9

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,945	MATTHIESSEN ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-46* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 and 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's cancellation of claims 1-19 and addition of new claims 20-46 in Paper No. 5 filed on 2 February 2001 is Acknowledged. Claims 20-46 are pending in the application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is indefinite because it is unclear if 'specific protease activity' as recited in the claim refers to the specific activity of the protein or to a 'specific' protease activity. As such, it is unclear as to what 'specific' protease activity is referred to by the claim. See same issue in claim 22, 28, 37, 40, 42 and 44.

Claim 32 is indefinite because of the use of both 'between' and 'approximately' to set a range. It is unclear as to whether 'between' or 'approximately' should be used in the range limitation set forth in the claim. See same issue in claim 42.

Claims 21-27, 29-39, 41 and 43-46 are indefinite for dependency on indefinite claims 20, 28, 40 or 42.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

4. Claims 28-32, 34 and 36-39 and 42-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Turecek *et al.* (US Patent 6,013,620). Turecek *et al.* teach a purification method of Factor VII from plasma (regarding claims 36 and 43 of the instant application) by absorption on anion exchange column (Q-Sepharose ® FF, Example 3; regarding claims 31-32 and 43-44 of the instant application) and on a hydrophobic column (Phenylsepharoase LS, Example 4 and column 5; regarding claims 34 and 44 of the instant application). The eluted fraction of Example 3 contains 89 U/mg amidolytic activity, that of Example 4 contains 276 U/mg amidolytic activity (see column 3 lines 50-55, table 1 and claim 1; regarding claims 28-30, 37 and 42-44 of the instant application). The elutions are carried out using buffers at pH 7.4 and without blood coagulation inhibitors (regarding claims 29-30 and 42 of the instant application). Turecek *et al.* teach the flow rate of the chromatography step of the purification method on the Q Sepharose ® FF column as 5.3 ml/min which corresponds to at least 1.7 column volumes per minute (Example 5; regarding claims 31-32 and 42 of the instant application). Turecek *et al.* teach the preparation of a pharmaceutical preparation made from Factor VII purified from the method

described above (Examples 3-14; regarding claims 38, 39, 45 and 46). Thus, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigma Chemical (Product F6509), in view of Thomas (US Patent 4,456,591), Broze *et al.* (J. Biol. Chem. 1980 255: 1242-1247), Berkner *et al.* (US Patent 6,039,944), Thomas (US Patent NO 4,357,321), Turecek *et al.* (US Patent 5,93,968) and Scopes (Protein Purification, Springer-Verlag New York, 1987, pages 251).

The Sigma Chemical Company product catalog of 1997 lists a Factor VII preparation (product No: F6509) with a VIIc/VIIam ratio of 0.9-1.5 and a specific activity of 1000-2000 U/mg of protein. A VIIc/VIIam ratio of 1.5 indicates less than 5% of Factor VIIa. (Regarding claims 20-21.) The volume may be adjusted to an activity between 5 and 5,000 U/ml (regarding claim 22). Factor VII was recovered from normal plasma (regarding claim 26).

The Sigma product contains the inhibitor benzamidine in the composition.

Thomas teaches the purification of Factor VII in which Factor VII is purified prior to activation to Factor VIIa (column 3, line 60; Example 1). Factor VII with an activity of 3,250 U/mg of protein is purified from benzamidine (Example 1). Once activated, the Factor VIIa is

stable for 72 hrs (regarding claim 24). Factor VII was recovered from normal plasma (regarding claim 26).

Broze *et al.* teach the purification of blood coagulation Factor VII to apparent homogeneity with undetectable levels of activated Factor VII or Factor VIIa (see Abstract and Figure 4). The Factor VII preparation was freed from benzamidine, a potential inhibitor of blood coagulation, by gel filtration (page 1244, line 3). The final preparation of Factor VII had a specific activity of 2.3 units/μg and approximately 57 units/μg (20-25 fold increase when activate; see page 1244, second column) when activated, indicating less than 5% of Factor VIIa in the final preparation. Factor VII was recovered from normal plasma (regarding claim 26). The final sample of Factor VII was lyophilized and resuspended in inhibitor free solution (regarding claim 23); the volume may be adjusted to and activity between 5 and 5,000 U/ml (regarding claim 22).

Berkner *et al.* teach the production and purification of recombinant Factor VII (Example IV, regarding claim 25). The preparation is free of human pathogens (regarding claim 27).

Thomas teach Factor VII in combination with Factor IX and X for the treatment of clotting factor inhibitors (see Abstract).

Scopes teach the use of glycerol solutions and a stable medium for the storage and handling of proteins (regarding claim 20). A glycerol solution is used to resuspend protein without the need of other stabilizers.

Turecek *et al.* (1997) and references therein teach the method of removing pathogens from blood coagulation factor compositions involving the lyophilization of the protein.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to further purified the Factor VII protein sold by the Sigma Chemical Company away from benzamidine as was done in the Factor VII preparations of Broze *et al.* and Thomas (regarding claims 20 and 21). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to recover the protein from human plasma (as done by Sigma, Broze *et al.* and Thomas) or recombinantly (as done by Berkner *et al.*), the latter preparation would be free of human pathogens (regarding claim 25-27). The preparation may be lyophilized as taught by Broze *et al.* and Turecek *et al.*, resuspended to an activity of 5 U/ml in a stable solution, such as a glycerol as taught by Scopes, and would be stable for up to 72 hours as taught by Thomas (regarding claims 22-24). The Factor VII composition could also contained Factor IX and X as taught by Thomas (regarding claim 40-41) and could be treated for the removal of human pathogens as taught by Turecek *et al.* (regarding claim 27).

The person of ordinary skill in the art would have been motivated remove the presence of the protease inhibitor benzamidine because the protein of interest is a protease inhibitor and would interfere with the activity of the activated Factor VII. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine Factor VII with the Factor IX and X because this combination has been used to treat human disorders.

The person of ordinary skill in the art would have expected success because the composition was known in the art and the methods of handling protein (*e.g.*, lyophilization, recombinant purification), the desired level of specific activity (50 and 100 units/mg protein), and composition (*e.g.*, free of inhibitors and pathogens, combination compositions) are known in

the art. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

7. Claims 28-39 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turecek *et al.* (US Patent No: 6,013,620), in view of Jorgensen *et al.* (US Patent 5,700,914), Goldfarb *et al.* (J. Biol. Chem. 1998 273: 2866-2873) and Scopes (Protein Purification, Springer-Verlag New York, 1987, pages 119-126).

Turecek *et al.* teach a purification method of Factor VII from plasma (regarding claims 36 and 43 of the instant application) by absorption on anion exchange column (Q-Sepharose FF, Example 3; regarding claims 31-32 and 43-44 of the instant application) and on a hydrophobic column (Phenylsepharoase LS, Example 4 and column 5; regarding claims 34 and 44 of the instant application). The eluted fraction of Example 3 contains 89 U/mg amidolytic activity, that of Example 4 contains 276 U/mg amidolytic activity (see column 3 lines 50-55, table 1 and claim 1; regarding claims 28-30, 37 and 42-44 of the instant application). The elutions are carried out using buffers at pH 7.4 and without blood coagulation inhibitors (regarding claims 29-30 and 42 of the instant application). Turecek *et al.* teach the flow rate of the chromatography step of the purification method on the Q Sepharose ® FF column as 5.3 ml/min which corresponds to at least 1.7 column volumes per minute (Example 5; regarding claims 31-32 and 42 of the instant application). Turecek *et al.* teach the preparation of a pharmaceutical preparation made from Factor VII purified from the method described above (Examples 3-14; regarding claims 38, 39, 45 and 46).

Turecek *et al.* does not teach purification of factor VII on an immunoaffinity column specific for Factor VII (regarding claim 33). Turecek *et al.* does not teach the use of a hydrogel substrate (regarding claim 35) or the purification of Factor VII from cell culture (regarding claim 36).

Jorgensen *et al.* teach the purification of Factor VII from recombinant cells (regarding claim 36 and 43) using anion exchange followed by immunoaffinity columns specific for Factor VII (Example 3; regarding claim 33).

Goldfarb *et al.* teach protein purification on a hydrogel (regarding claim 35).

Scopes teaches the general principles and procedures of protein purification. Scopes teaches the general principle of flow rates and elution time and the need to optimized these parameters depending on column substrate and size and protein that is being purified. The protein of interest can be detected along an elution profile in which elution time, ionic strength and pH of the buffer may be adjusted (Chapter 5, especially pages 120-121; regarding claims 31-32 and 42; see also Pharmacia Biotech Q Sepharose Fast Flow Instructions, August 1996).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the hydrophobic column used by the method of Turecek *et al.* for the immunoaffinity column specific for Factor VII taught by Jorgensen *et al.* and to substitute the column for a hydrogel as taught by Goldfarb *et al.*. Additionally, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute plasma used as starting material in the method taught by Turecek *et al.* for the cells and cell culture medium taught by Jorgensen *et al.*. The person of ordinary skill in the art would have been motivated and would have expected success in using the immunoaffinity column or

hydrogel in the purification of Factor VII because such these are common in the art of protein purification and the column specific for Factor VII was known and shown to be effective in the purification of Factor VII (Jorgensen *et al.* and Goldfarb *et al.*). The person of ordinary skill in the art would have been motivated and would have expected success in using a recombinant cell culture as starting material for the purification of Factor VII because producing recombinant proteins is an efficient means of producing protein and it had been demonstrated that of recombinant Factor VII is effective (Jorgenson *et al.*).

Because the methods of producing the products of claims 38, 39, 45 and 46 is obvious as shown above, the products produced by the methods are also obvious in regards to product by process. Thus the claimed invention was also within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Advisory Information

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: JH Lawson and KG Mann. Cooperative activation of human factor IX by the human extrinsic pathway of blood coagulation. J. Biol. Chem. 1991 266: 11317-11327. Lawson *et al.* use purified human factor VII from Haematologic Technologies, which is sold as a zymogen or active enzyme. The Factor VII zymogen sold by Haematologic Technologies is contained in a glycerol solution free of inhibitors. The activated Factor VIIa made from the above zymogen has a specific activity of 16,000 U/mg.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-3975 for regular communications and (703) 746-3975 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
September 30, 2002
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